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Oxygen and nitrous oxide uptake during general anaesthesia for cardiac catheterization in infants with congential heart disease[1]

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Oxygen and nitrous oxide uptake has been measured in 22 infants with congenital heart disease during general anaesthesia for cardiac catheterization involving curarization, and manual pulmonary hyperventilation using a closed circuit apparatus designed for this purpose.

A highly significant relation was found between oxygen uptake and patient surface area given by the regression equation $\dot{V}_{O_2} = 16{\cdot}5$ *(body weight in kg)*$^{2/3} - 3{\cdot}8$ *ml/min (mean* $\dot{V}_{O_2} = 165$ *ml/min/m*^{2}*), and between* $\dot{V}_{O_2}$ *and body weight given by* $\frac{\dot{V}_{O_2}}{kg} = 6{\cdot}74e^{-0{\cdot}076\,kg} + 4$. *Values for* $\dot{V}_{O_2}$ *varied from 10 ml/min per kg to 5 ml/min per kg for a body weight range of 3 to 22 kg.*

Nitrous oxide uptake decreased with time from induction of anaesthesia given by the highly significant regression equation $\frac{\dot{V}_{N_2O}}{kg} = 5{\cdot}69e^{-0{\cdot}0489\,t}$ *and the total nitrous oxide uptake in ml/kg body weight at any time t is given by* $\frac{V_{N_2O}}{kg} = 116\,(1 - e^{-0{\cdot}0489\,t})$. *These figures reveal a mean tissue mass reduction in our patients of 38 per cent of normal, a figure that compares well with the observation based on body weight of a 33 per cent reduction below the 50th percentile. These patients equilibrate with nitrous oxide 1·6 times as fast as subjects of normal weight.*

The majority of infants in this unit undergo cardiac catheterization during general anaesthesia, involving neuromuscular paralysis with curare, endotracheal intubation, and manual pulmonary ventilation with oxygen and nitrous oxide. We have been unable to find any information on observations of oxygen uptake carried out under the above conditions. Cardiac output calculations and shunt flows are usually made using an assumed oxygen uptake based upon values observed in sedated infants breathing oxygen from an open circuit (Cayler, Rudolph, and Nadas, 1963; Lees, Way, and Ross, 1967) or in awake infants via a closed circuit (Levison, Delivoria-Papadopoulos, and Swyer, 1965). None of these methods is suitable for use during general anaesthesia, because the classical closed circuit spirometric method cannot be used in the presence of nitrous oxide, since the uptake of this gas cannot be distinguished from that of oxygen.

It has also been suggested that there is little justification in assuming oxygen uptake values from data in the spontaneously breathing infant, since these are rarely basal during general anaesthesia (Nunn, Bergman, and Coleman, 1965). One object of this paper is to report values during general anaesthesia. Since nitrous oxide forms the balance of the inspired gas, it seemed essential to study its behaviour also, since no published information on this important point is available.

We therefore devised a closed circuit apparatus for this purpose, and this paper reports its use in a group of infants with congenital heart disease studied during general anaesthesia and intermittent positive pressure ventilation.

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Method

The closed circuit apparatus used to measure oxygen and nitrous oxide uptake is a modification

of that previously described by us in detail (Owen-Thomas, Meade and Jones, 1970; Owen-Thomas *et al.*, 1971). The quantity of oxygen taken up by the lungs is given by the difference between circuit initial and final oxygen concentration and the volume change of the circuit as indicated by the measured change in volume of a bag in a bottle attachment within the circuit, divided by the time of measurement. Carbon dioxide produced by the patient was absorbed from the circuit by soda lime. Before each measurement of oxygen and nitrous oxide uptake, the circuit was filled with 33 per cent oxygen and 67 per cent nitrous oxide, and once oxygen uptake had been measured, nitrous oxide uptake was given by the change in volume of the circuit minus oxygen uptake, divided by the time of measurement. In order to measure the rate of uptake of nitrous oxide in each patient, the time from induction for each observation was noted.

Patients

Premedication consisted of atropine 0·1 mg to 0·6 mg by intramuscular injection in infants up to 1 year of age and above this age, morphine 0·33 mg per kg was added by intramuscular injection. General anaesthesia was induced by intravenous injection of 2·5 per cent sodium thiopentone, 4 mg per kg, and neuromuscular paralysis was achieved by intravenous injection of d-tubocurarine 0·6 mg per kg. The trachea was intubated with

TABLE *Oxygen and nitrous oxide uptake in 22 infants with severe congenital heart disease*

Case No.	*Age*	*Weight (kg)*	*Diagnosis*	*Oxygen uptake* (ml/min per kg)*	*Nitrous oxide uptake (ml/min per kg)*
1	2 mth	3·4	Persistent ductus arteriosus	8·9	2·4
				8·0	0·7
				8·2	0·4
					0
2	7 yr	14·5	Pulm. hypertension	5·8	0
				4·4	
3	10 dy	2·7	Transposition of vessels	5·7	3·0
				5·1	1·4
					6·6
4	5 mth	6·4	Fibroelastosis	10·8	0·0
				8·3	
				9·0	1·7
5	1 yr	9·5	Transposition of great vessels	8·1	1·8
				6·3	0·9
6	2 yr	10·0	Transposition of great vessels	8·3	2·1
				7·9	0·9
					0·6
7	4 mth	4·1	Transposition of great vessels	9·6	
				8·2	5·7
8	8 mth	6·9	Persistent ductus arteriosus	9·4	1·0
				9·0	0·9
9	2 mth	3·8	Persistent ductus arteriosus, ventric. septal defect	8·3	5·3
				8·2	0·6
					0·1
10	4 yr	15·2	Fallot's tetralogy	6·3	0·0
				6·0	3·9
				6·6	3·0
11	3 yr	14·2	Fallot's tetralogy	7·0	0·4
				5·3	
				5·9	3·7
				7·1	1·5
				5·9	3·3
12	3 mth	3·7	Ventricular septal defect	10·2	0·8
				10·3	0·4
13	14 mth	5·9	Ventric. septal defect	8·9	4·6
				8·8	1·5
				9·1	6·8
				9·0	0·4
				9·0	0·0
14	8 mth	5·6	Coarctation of aorta	7·4	1·7
				6·9	1·8
				7·0	0·9
				6·8	
15	1 mth	1·9	Mitral stenosis and incompetence	7·4	2·1
				5·7	0·9
				7·4	0·6
16	2 mth	3·6	Transposition of great arteries	7·5	5·7
				7·6	1·0
				8·3	0·9
17	10 dy	3·2	Ventric. septal defect	6·2	5·3
				5·8	0·6
				5·7	
18	6 mth	4·5	Transposition of great arteries, persistent ductus arteriosus, atrial septal defect	10·9	0·1
				10·4	0·0
				10·6	3·9
				10·8	3·0
19	12 dy	3·7	Transposition of great arteries	5·6	0·4
				3·9	3·7
				6·0	1·5
20	10 dy	2·5	TAPVD†	7·1	3·3
				5·8	0·8
21	3 wk	3·2	TAPVD†	7·1	0·4
			Persistent ductus arteriosus	6·5	
				6·1	4·6
22	8 yr	22·0	Aortic stenosis	5·8	1·5
				5·4	6·8
				5·3	0·4
				5·1	0·0
				5·1	

$\dot{V}_{O_2}$ values for Cases 1–12 are from Owen-Thomas *et al.* (1971), reproduced by kind permission of the Editor, *British Journal of Anaesthesia*.

TAPVD = Total anomalous pulmonary venous drainage.

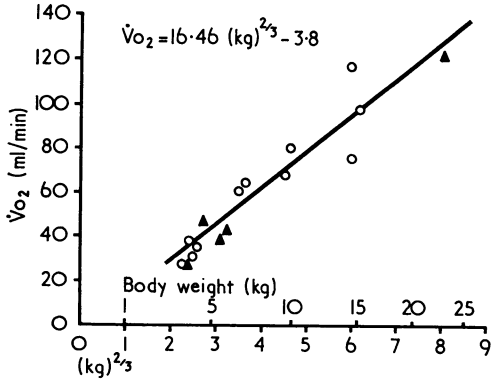
a closely fitting rubber endotracheal tube, and the pharynx and oro-pharynx filled with sterile water. The lungs were then hyperinflated to a tracheal pressure of 35–45 cmH_2O, and if bubbles appeared in the pharynx reintubation was performed with a closer fitting tube and the test repeated. The results reported here are from patients in whom no leaks were observed. Patients were studied lying supine on the radiography table. The probe of an oesophageal thermometer was placed in the middle third of the patient's oesophagus, its position confirmed by screening, and temperature was monitored throughout each study. Patients aged less than 6 months were wrapped in gamgee wool and polyethylene. No attempt was made to conduct studies in a neutral thermal environment, room temperature being 24–26°C throughout the studies. Oxygen and nitrous oxide uptake measurements were made over 3 minutes in the older children and up to 20 minutes in the newborn infants. An attempt was made to ensure a comparable drop in circuit concentration of 3 per cent of its initial value in each patient.

Results

Observations were carried out in 22 patients ranging in age from 10 days to 8 years and in body weight from 1·87 kg to 2·2 kg (Table). Sixty-five oxygen uptake measurements were made, an average of three recordings per patient. Nitrous oxide measurements were carried out in Cases 13 to 22.

Oxygen uptake This was measured in 22 patients of whom 6 were newborns, and the results are shown in Fig. 1 and 2. Fig. 1 shows that the oxygen consumption is proportional to surface area $[\sqrt[3]{(\text{body weight})^2}]$[1]. The regression equation for this relation, based upon

FIG. 1 *This shows a linear regression for oxygen uptake against body weight* $kg^{2/3}$. *Note that surface area can be read directly from body weight on the horizontal axis.* O, ▲, *results of 2 studies separated by an interval of 3 months.*



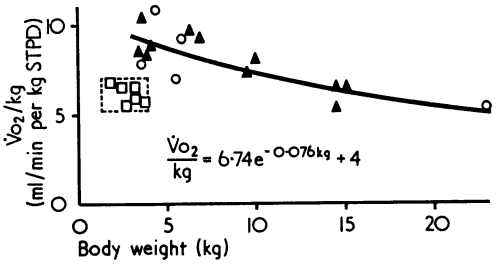


FIG. 2 *Oxygen uptake is shown plotted against body weight. The insert shows a group of 6 newborn infants.*

our observations, is given in ml/minute by,

$$\dot{V}_{O_2} = 16{\cdot}5 \text{ (body weight in kg)}^{2/3} - 3{\cdot}8 \quad (1)$$

where the correlation coefficient, $r = 0{\cdot}95$, $t = 11{\cdot}3$, and $P < 0{\cdot}001$, with a standard error of the estimate of 9·2 ml/min.

This relation suggests that oxygen uptake per kilogram body weight also varies with body weight which is confirmed in Fig. 2. Oxygen uptake per kilogram is shown to fall continuously as body weight increases. An exponential regression has been fitted which declines asymptotically to an assumed adult normal value of 4 ml/min per kg body weight,

$$\frac{\dot{V}_{O_2}}{kg} = 6{\cdot}74e^{-0{\cdot}076\,kg} + 4 \quad (2)$$

where, $r = 0{\cdot}84$, $t = 5{\cdot}8$, $P < 0{\cdot}001$, and standard error of the estimate $= \pm 22$ per cent.

Values for oxygen uptake vary from 10 ml/min per kg to 5 ml/min per kg for a body weight range of 3 to 22 kg.

The 6 neonates had $\dot{V}_{O_2}$ values which clearly differed from the other patients studied (mean neonatal $\dot{V}_{O_2} = 6{\cdot}2$ ml/min per kg). Therefore they were excluded from the regression analysis. They are shown in the dotted inset (Fig. 2) and lie below the values for the other patients of similar weight but who are older than one month.

Body weight There is evidence that infants with severe congenital heart disease are under weight with respect to age (Mehrizi and Drash, 1962; Lees and colleagues, 1965) and Fig. 3 shows the relation between the body weight of our patients and their predicted weight at the 50th percentile. From this we derived the following regression equation,

$$\text{Observed body weight (kg)} = 0{\cdot}78 \text{ (predicted body weight kg)} - 0{\cdot}25 \quad (3)$$

This relation is highly significant as given by the correlation coefficient of 0·93 ($t = 9{\cdot}6$,

[1] Surface area in metres$^2 = 0{\cdot}1\sqrt[3]{\text{body weight}^2}$ (Lowe's equation as quoted by Nelson and colleagues, 1969).

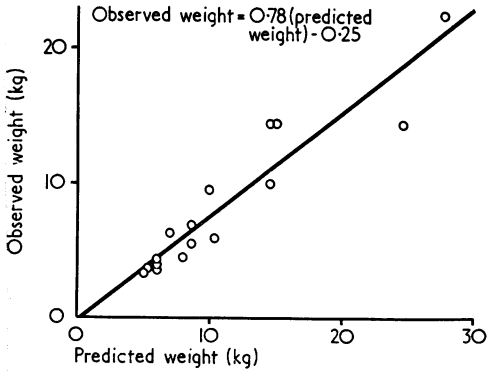


FIG. 3 *The relation between observed and predicted patient body weight.*

$P < 0{\cdot}001$, and the standard error of the estimate = 1·97). The intercept (−0·25) is negligible, so that it may be concluded that the weight of our patients is 78 per cent of the predicted normal value. The relevance of this finding to nitrous oxide uptake will be discussed later.

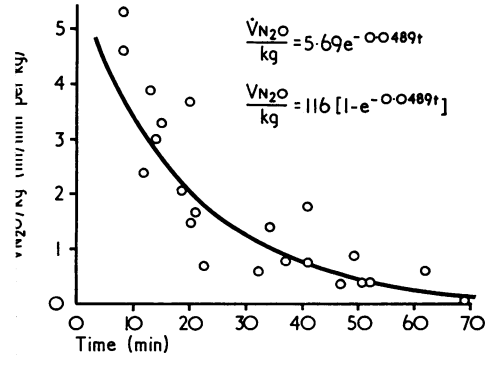
Nitrous oxide uptake This was measured in 10 subjects (Cases 13 to 22, Table), 5 of whom were neonates. The results are seen in Fig. 4 which shows that the rate of nitrous oxide uptake decreases with time from the induction of anaesthesia (t). The regression equation denoting this relation is given by,

$$\frac{\dot{V}_{N_2O}}{kg} = 5{\cdot}69e^{-0{\cdot}0489t} \qquad (4)$$

The relation is highly significant as indicated by the correlation coefficient $r = 0{\cdot}88$, $t = 8{\cdot}4$, $P < 0{\cdot}001$).

The integral of this equation gives the total

FIG. 4 *Rate of nitrous oxide per kg body weight related to time from induction of anaesthesia in 10 infants.*



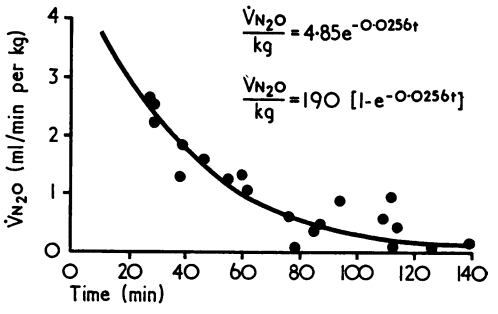


FIG. 5 *Rate of nitrous oxide uptake per kg body weight related to time from induction in 13 anaesthetized adult rabbits.*

nitrous oxide uptake in ml/kg body weight at any time, t

$$\frac{V_{N_2O}}{kg} = 116\,(1-e^{-0{\cdot}0489t}) \qquad (5)$$

Previous animal experiments carried out using a similar circuit for the measurement of nitrous oxide uptake (Owen-Thomas *et al.*, 1970) show a similar regression relation for the rate of uptake to that of our infants (Fig. 5), but the significance of the difference in total nitrous oxide uptake will be discussed below.

Discussion

Oxygen uptake We have shown that oxygen uptake in our patients is proportional to body surface area. Using the Lowe equation (see footnote page 54), the mean oxygen consumption of our patients excluding the neonates was 165 ml/min per m^2. With the exception of one 22 kg patient, the surface area of our patients was in the range 0·20–0·5 m^2. In this range, Cayler *et al.* (1963) reported a mean oxygen uptake of infants with congenital heart disease of 198 ml/min per m^2, but these were experiments carried out during cardiac catheterization without general anaesthesia. Our values are 17 per cent lower than those of the above workers, and it is possible that this is due to the complete neuromuscular paralysis in our patients during the investigation, which could be a measure of the difference in oxygen uptake between curarized muscle and resting muscle. We have also shown (Fig. 2) that over the weight range 3 to 22 kg, oxygen uptake per kg body weight falls from 10 to 5 ml/min per kg. Clearly, considerable error could arise in the estimation of cardiac output if a mean (fixed) value for $\dot{V}_{O_2}$/kg were used.

The measurements for neonates are clustered about a mean value of 6·2 ml/min per

kg (STPD). All our patients had an oesophageal-ambient temperature gradient of 10°C, and for this gradient one would expect an oxygen consumption of 10–15 ml/min per kg during spontaneous respiration, whereas in a neutral thermal environment a figure of 4·6 ml/min per kg would be appropriate (Scopes, 1966; Dawes, 1968). The relatively low values which we measured could be due again in part to the diminished oxygen consumption of paralysed muscle.

Nitrous oxide uptake The exponential decline in the rate of nitrous oxide uptake with time begins not later than 10 minutes from the induction of anaesthesia. At this time there is a steady state in which the nitrous oxide tension in the blood is constant and is virtually identical with that of the inspired gas; in addition, the rate of diffusion of nitrous oxide into the tissues is proportional to the blood/tissue tension gradient.

The coefficient of equation 4 extrapolates these conditions back to time zero when the tissue tension of nitrous oxide is zero. Therefore the coefficient (5.69) is numerically equal to the diffusion coefficient × the nitrous oxide tension in the blood (0·67 atmospheres). That is, 5·69 = diffusion rate/kg tissue per kg body weight × 0·67. Therefore, the diffusion rate of nitrous oxide into the tissues per kg tissue, per kg body weight, per atmosphere tension gradient is 5·69/0·67 = 8·5 ml/min per kg tissue per kg body weight. Nitrous oxide is a highly soluble and therefore highly diffusible gas, and it can be easily shown that the rate of diffusion of nitrous oxide through the lungs per atmosphere gradient, per kg body weight is of the order of 400 times this value of 8·5 shown above. Body capillary surface area is unlikely to be less than that of the pulmonary capillaries. Thus, the rate of diffusion into the tissues is very low and probably relates to the mean length of diffusion path between tissue capillaries.

Equation 5 relates total nitrous oxide uptake with time of absorption, and the coefficient (116) is the uptake in ml/kg body weight at final equilibrium (t = infinity).

Therefore, if

0·4 = solubility of nitrous oxide in tissue in volumes nitrous oxide per volume of tissue, per atmosphere tension,

V_t = volume of tissues in ml and

0·67 = tension of nitrous oxide in blood and tissues in atmospheres,

then, $$116 = \frac{0{\cdot}4 \times V_t \times 0{\cdot}67}{\text{body weight}}$$

Therefore tissue volume per kg body weight

$$= \frac{116}{0{\cdot}4 \times 0{\cdot}67} = 434 \text{ ml/kg body weight}$$

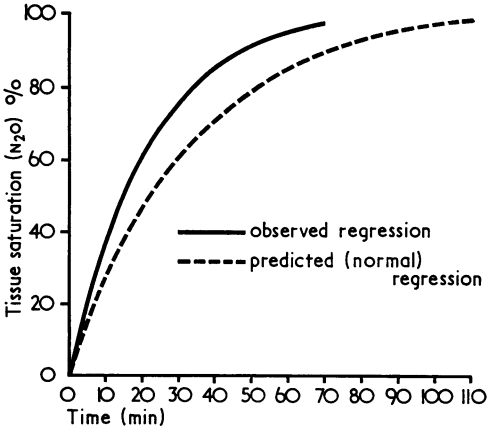
If the normal tissue volume is 70 per cent of body weight, i.e. 700 ml per kg body weight, then the mean tissue volume of our group of infants is $\frac{434}{700} \times 100 = 62$ per cent. Thus, the tissue mass of our patients appears to be reduced by 38 per cent. This estimate is confirmed by our observations of the patient's weight. It has already been shown (equation 3) that their weight is 78 per cent of normal. If this reduction is assumed to be due to tissue loss, the non-fluid tissue fraction (0·3) remaining unaltered, then the tissue mass as a fraction of normal is given by

$$\frac{0{\cdot}78 - 0{\cdot}3}{0{\cdot}7} = 0{\cdot}67 = 67 \text{ per cent of normal,}$$

corresponding to a tissue loss of 33 per cent which is to be compared with the 38 per cent deduced from our nitrous oxide data.

Experiments on healthy rabbits (Owen-Thomas and colleagues, 1970) (Fig. 5) revealed a total uptake coefficient of nitrous oxide of 190 ml/kg body weight, and gives a tissue volume of 710 ml/kg body weight, the normal value. This is further experimental evidence that calculations based upon the nitrous oxide uptake afford a valid measure of tissue volume. Variation in tissue volume/body weight ratio also affects the rate of uptake of nitrous oxide, i.e. the time taken to reach a given level of saturation. It can be seen that when a gas diffuses at constant ambient pressure into a space of finite volume, then the time constant of the diffusion rate is

FIG. 6 *Regression lines for tissue saturation with nitrous oxide on time from induction of anaesthesia, based upon observed values and predicted normal values.*



the ratio of the diffusion constant to the volume into which the gas is diffusing. Thus, the exponent of equation 5 will vary inversely as the tissue volume/kg body weight, so that the time to reach any given saturation with nitrous oxide will vary directly as the tissue volume/kg body weight. In our group of infants, the tissue volume/body weight ratio is 62 per cent of normal, so that they will reach a given saturation with nitrous oxide in only 62 per cent of the time that a normal infant would take.

This point is illustrated in Fig. 6, where the observed regression for saturation was, tissue saturation with nitrous oxide $= 1 - e^{-0.0489t}$, corresponding saturation on the normal curve being $1.6 \times t$. Underweight subjects will equilibrate quicker with nitrous oxide than subjects of normal weight.

The nitrous oxide technique affords an accurate and simple method of measuring tissue volume. It may prove to be of value in assessing the effect of the cardiac lesion on metabolism and the influence of operative and other therapeutic measures.

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